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Theoretical study on physicochemical and geometrical properties of Doxorubicin and its different carriers such as PEG-FOL and PEO-b-PCL

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ABSTRACT

The physicochemical properties of Doxorubicin - PEO-b-PCL (Doxorubicin conjugated to poly(ethylene oxide)-block-Poly(epsilon-caprolactone)) and Doxorubicin–PEG–FOL(Doxorubicin conjugated to polyethylene glycol–folate) have been estimated using Density functional Theory (DFT) and Hartree Fock(HF) calculations.In this report some geometrical parameters of DOX-PEO-b-PCL complex of the conjugated complex and DOX–PEG–FOL complex of the conjugated complex were investigated using computational methods and physicochemical properties such as Gibbs free energy of solvation ($\Delta G_{solvation}$),binding energy, partition coefficient, and Dipole Moment (DM) of complexes were investigated . Our results indicate that water-solubility of Doxorubicin–PEG-FOL is higher than that of Doxorubicin .

Keywords: Anti-cancer drugs; Molecular geometry; Doxorubicin-PEO-b-PCL; Doxorubicin-PEG-FOL

INTRODUCTION

Doxorubicin is an anthracycline ring antibiotic that is widely used as a cancer therapeutic[1]. The scheme of DOX is in Fig1.

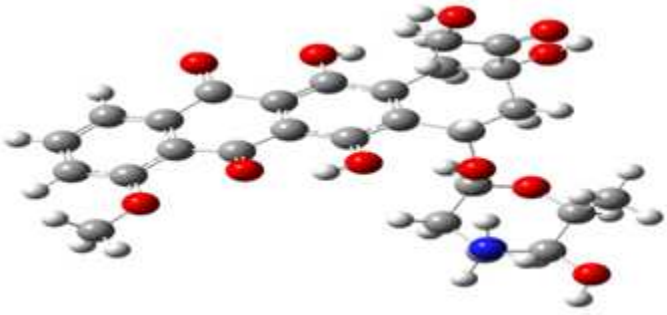

Fig.1.Doxorubicin

Drug delivery technology (DDT) is increasingly important as a component of drug development. With an increasing diversity of compounds addressing more drug targets, the available range and sophistication of DDTs has expanded with the goal of increasing the successful rate of new chemical entities. There are many approaches to drug delivery via drug/drug carrier combinations, such as encapsulation, hydrogel formation, nanoaggregation, and micellar delivery. For doxorubicin delivery, encapsulation and micellar delivery have received increased attention because this system can protect and carry the drug directed to its intended target.

In experimental studies carried out by some other researchers,it has been illustrated that development of new dosage forms that can change the normal fate of drugs in a biological system and direct them toward their cellular or sub-cellular targets has been the focus of many pharmaceutical research efforts during the past few decades. Chemical conjugation of DOX to the polymeric micellar core in PEO-b-P(CL-DOX) is expected to reduce the chance of premature drug release outside tumor tissue. On the other hand, since PCL backbone is prone to hydrolysis especially in acidic environment, core degradation followed by micellar dissociation and release of DOX-caprolactone (DOX-CL) derivatives may be facilitated in the acidic environment of the edosome/lysosomes after endocytosis of PEO-b-P(CL-DOX) micelles by tumor cells[2-4]. DOX-PEO-b-PCL complex was synthesized by Abdullah Mahmud and colleagues[5] . The conjugation scheme is in Fig. 2

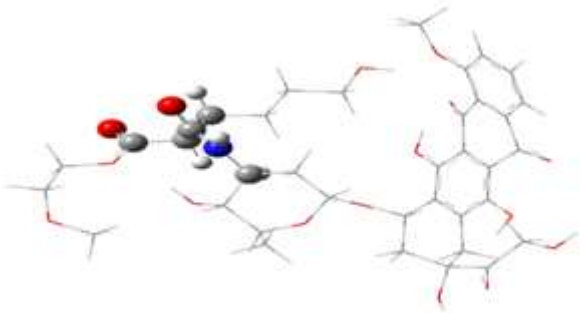

Fig.2. DOX-PEO-b-PCL

In experimental studies carried out by some other researchers,it has been illustrated that for folate-receptor-targeted anti-cancer therapy, doxorubicin aggregates in a nano-scale size were produced employing doxorubicin–polyethylene glycol–folate (DOX–PEG–FOL) conjugate[6].In DOX–PEG–FOL complex ,Doxorubicin and folate were respectively conjugated to α- and N-terminal end group of a PEG chain. DOX–PEG–FOL complex was synthesized by Hyuk Sang Yoo and colleagues[6] . The conjugation scheme is in Fig. 3. In order to understand the biological and anti cancer activity of these complexes, it is inevitable to study the physicochemical properties of doxorubicin-carrier conjugates. Therefore we used B3LYP calculations via Gaussian 03 [7] to study these properties. Complex DOX–PEG–FOL and DOX-PEO-b-PCL are large molecules. For large reactive systems, the calculation of energies can be simplified by treating the active part with a high-level quantum mechanical (QM) ab initio or density functional. One such method is the original ‘‘Our-own-N-layer Integrated molecular Orbital, Molecular Mechanics ONIOM’’ approach. We used of this approach for optimization of complex DOX–PEG–FOL and DOX-PEO-b-PCL.

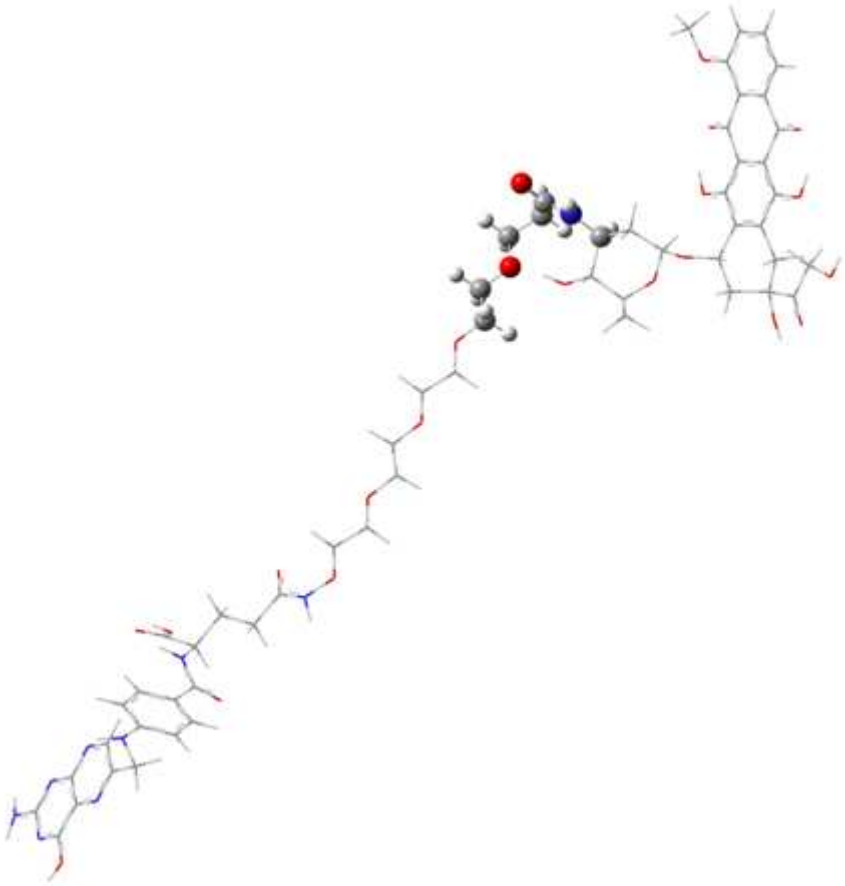

Fig.3.DOX-PEG-FOL

RESULTS AND DISCUSSION

The geometry structure of these two complexes were optimized at B3LYP/6-311++G** and HF/6-31G* level of theory and then the Gibbs free energy of solvation ($\Delta G_{solvation}$) were calculated at B3LYP/6-31*G level of theory[8] using Gaussian 03. Table 1 presents the geometrical parameters of two different complexes mentioned above around linking position (amide group), see also Fig 4.

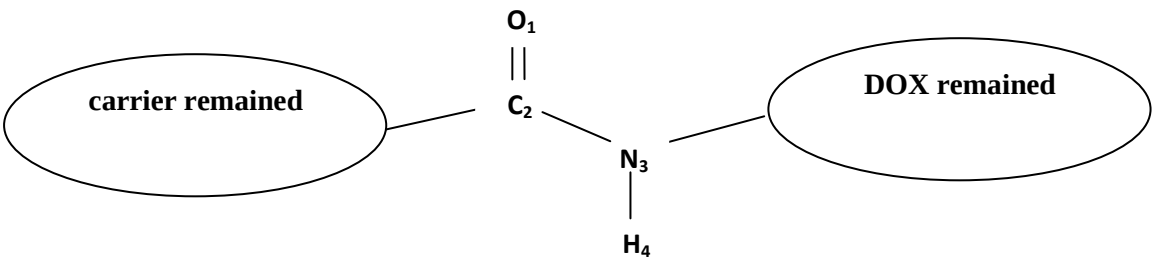

Fig 3. Structure of linking position in DOX-carrier complexe

Table 1. Geometrical parameter(bond lengths and bond angles) of complexes around linking position

complex	C2=O1 (Å)	C2-N3 (Å)	N4-H4 (Å)	C2-N3-H4 (°)
DOX-PEO-b-PCL	1.220	1.369	1.013	111.962
DOX-PEG-FOL	1.223	1.363	1.012	112.437

some physicochemical properties of DOX-PEO-b-PCL and DOX-PEG-FOL conjugates such as Refrectivity, polarizability, Log p, Hydration energy ,binding energies (BE), Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) are obtained from optimal structure[9] which have been shown in Table 2.

The 1-octanol/water partition coefficient is an important thermodynamic variable usually employed to understand and quantify the partitioning of solutes between aqueous and organic phases.

The logP is found according to equation (1). These values and the logP obtained from Hyperchem software[10] .in this report we calculeted logP by using Hyperchem software and equation (1) . These values presents in table 2.

From Gibbs free energies of solvation in two different phases at temperature T, one can calculate the corresponding partition coefficient, according to the following equation:

$$\log P = -\left(\frac{\Delta G_{sol,oct} - \Delta G_{sol,w}}{2.30RT} \right) \qquad (1)$$

Here R is gas constant and T is the temperature. The solvation free energy is used to compute the logP based on equation (1) and only solvation free energies in water and 1-octanol are needed to calculate log P.

Table 2. Some calculated physicochemical properties of DOX-PEO-b-PCL, DOX-PEG-FOL and Doxorubicin

physicochemical properties	DOX-PEO-b-PCL	DOX-PEG-FOL	Doxorubicin
Refrectivity[a]	185.66	296.89	135.50
polarizability	71.74	119.03	52.00
Log p[a]	-0.21	-0.77	-0.33
Log p[b]	0.109	-0.07	0.101
Hydration energy[a]	-27.39	-54.75	-24.03
Surface area[a](Å2)	834.12	1493.77	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-18.60	-54.25	-18.08
Dipole moment(Debye)	4.445	6.680	6.848
BE (ev/mol)	0.0545	-0.817	

[a]Data were calculated by using HyperChem 8 software[10]
[b]data were obtained by using eqation(1)

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of DOX-PEO-b-PCL, DOX-PEG-FOL and Doxorubicin .Regarding the calculation results, hydrophilicity of DOX-PEG-FOL is higher than that of Doxorubicin ; this fact can be verified through the Gibbs free energy of solvation ($\Delta G_{solvation}$)obtained for DOX-

PEG-FOL using Gaussian 03. Our results indicate that DOX-PEG-FOL mentioned above can be used to improve anti cancer activity and water-solubility of Doxorubicin.

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